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Ackerknecht, Erwin H

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HISTORICAL NOTES ON CANCER*

by

ERWIN H. ACKERKNECHT, M.D.

Professor of the History of Medicine, University of Zürich

CANCER means to us today 'malignant growth'. In spite of this specification it is a notion comparable in its vagueness and all-embracing character only to the expressions 'fever' or 'plague', as they were used four hundred years ago, the former embracing then such diverse diseases as malaria, typhus, or typhoid, the latter being applied to any kind of deadly epidemic, be it smallpox, bubonic plague, or typhus. Yet it took several millennia to develop even this insufficiently defined group out of the mass of 'bad swellings' and 'ulcers' of former days. It is obvious that it is not possible to write today a history of cancer in the sense of a historical epidemiology to the same extent to which we can write now a history of malaria or plague, two diseases well known in their limits, cause and prevalence. All one can do is to give some elements of the history of human knowledge and opinions concerning cancer, which in some way reflect indirectly the existence of the disease.

The first task faced by medicine was to discover clinically and macroscopically the different forms of cancer and to unite them in some common notion; more recently some knowledge as to its microscopic morphology, its physiology and causative factors has been acquired and some new therapeutic agents have been discovered.

Paleopathological, that is, bone evidence, as to the prehistoric occurrence of cancer is rare and relatively late. Some osteosarcomata have been found in cave bears and pleistocene horses. The first tumours of this kind in man have been described in Egyptian skulls from the First (3400 B.C.) and Fifth (c. 2750 B.C.) Dynasties and from precolumbian Peru. Multiple myelomata are present in bones from neolithic Europe and precolumbian North America.

It is practically certain that some of the 'swellings' and 'ulcers' of skin, mamma and female genitalia—for a long time on account of their accessibility the best or only known forms of cancer—described in the *Egyptian papyri* (c. 1500 B.C.) were cancers. They were treated by excision or caustic salves—just as today. The same descriptions are encountered in the ancient medical writings of Mesopotamia, India and Persia.

We find the beginnings of our notion of cancer, like most of our medical notions, in the Hippocratic writings (c. 400 B.C.) where non-inflammatory, hard swellings and ulcers of the skin, female breast and genitalia with tendency to generalization, recidive and fatal ending are described under the names of *karkinos* or *karkinoma*, translated later into Latin as cancer. The expression

* The only more substantial essay on the history of cancer in English is to be found in J. Ewing, *Neoplastic Diseases*, Philadelphia, 1928. In German is available the treatise by Jacob Wolff, *Die Lehre von der Krebskrankheit von den ältesten Zeiten bis zur Gegenwart*, 4 vols., Jena, 1907–28.

skirros (Latin: *scirrhus*) occasionally also occurs. In later times this term found manifold and confusing uses as a name for non-cancerous hard tumours, precancerous tumours or particular species of cancers. Greek votives and works of art confirm the existence of cancer in ancient Greece. One famous Hippocratic aphorism warns against treatment of non-ulcerated cancer.

The same therapeutic pessimism prevailed with the Roman encyclopaedist Celsus (c. A.D. 1), though he reported radical operations of lip and breast cancer. He added penis cancer to the list of known cancers, and tried to differentiate cancer from benign tumours like lipoma, atheroma and steatoma. It is interesting to learn that Soranus (c. A.D. 100) observed cancer of the uterus with a speculum.

The last great physician of antiquity, Galen (c. A.D. 150), wrote a special book on 'tumours'. Among his sixty-one kinds of tumours Galen described oedema and erysipelas as well as lipoma and cancer. The confusion of cancer with other tumours explains at all times many reports of 'cancer cures', on which in turn at all times quacks have thrived. Galen approached our notion of neoplasm and malignant growth in one of his three categories of growth, the growth '*praeter naturam*', that is, outside of nature. (The other two were '*secundum naturam*', that is, corresponding to nature, and '*supra naturam*', quantitatively beyond nature.) To go beyond such brilliant speculations and arrive at our notion of cancer was wellnigh impossible to people who could not complement their clinical observations by gross pathological anatomy, not to speak of microscopy. Galen also made definite for the next 1,500 years the old theory which explained cancer as a disease of one of the four basic tumours of the human body, the (inexisting) black bile, the *melan cholos*. As long as such an interpretation of cancer as a primary diathesis, local only in its manifestations, prevailed, it was bound to discourage surgery even beyond the effect of poor practical results, and encourage general treatments like dieting, drugging or bleeding, which prevailed far into the nineteenth century.

The Middle Ages could not add much to our knowledge of cancer, though the field of known cancers, especially internal ones, widens continuously. Among the Arabs we find Rhazes (c. A.D. 900) differentiating nasal polyps and cancer, Avenzoar (c. 1150) suggesting nutritional clysters and sound feeding in the case of the slowly emerging cancers of oesophagus and stomach, known probably first to Galen. Salernitan surgeons (c. A.D. 1100) describe cancer ('fungus') of the dura mater and the testicle, and suggest rectal examination as a routine procedure when rectal cancer is suspected. Medieval surgeons are just as divided and often as sceptical as to the desirability of surgical procedures in cancer as were those of antiquity. The medieval separation of surgery and medicine certainly did not facilitate progress in our field.

The Renaissance of the sixteenth century adds relatively little to oncology; the great Vesalius wrestles with the knotty problem of clinical differentiation of tumours; Ambroise Paré underlines the occurrence of metastases, interpreting them, of course, in the traditional humoralistic fashion as local manifestations of the 'melancholic' diathesis. Important new tendencies appear only in the

seventeenth century. Marco Aurelio Severino and Tulpus (the object of Rembrandt's famous painting) publish a certain number of data on the gross pathological anatomy of cancers. On the basis of such studies Tulpus was able to diagnose a cancer of the bladder *in vivo*. In connection with the newly discovered lymphatic system the French philosopher-mathematician-physician Descartes replaces Galen's 'black bile' theory of cancer through a widely acclaimed mechanistic lymph theory. Others look in newly acquired chemical notions (acidity) for an explanation of the disease. The lymph theory had positive aspects as in the long run it would favour removal of cancerous lymph glands. Most detrimental for sufferers from cancer was the widely adopted opinion of two prominent seventeenth-century clinicians, Sennert and Zacutus Lusitanus, that cancer is contagious, an opinion arrived at through analogies with other 'tumours' like leprosy and elephantiasis. It barred cancer patients from many hospitals up to the middle of the nineteenth century. We remind our reader in this context of the dramatic conflict of James Marion Sims with the managers of the Women's Hospital in New York in 1874.

The essential contribution of the eighteenth century to general pathology, the turn from humoralistic diathesis to solidistic localism, was also applied to oncology with particularly important practical and theoretical consequences. The great promotor of localism, Morgagni, himself described numerous cancers from this point of view. Emphasis on local beginnings and lymphatic spread of cancer was the keynote of the important monograph of the French surgeon Le Dran (1757). Bernard Peyrilhe (1735–1804) was the first to try transplantation of cancerous tissue into an animal, the dog. The elimination of the latter by drowning by an irate housekeeper on account of its loud protestations deprived us of the results of this first experiment. Peyrilhe added the newly discovered carbon dioxide and carrot juice to anti-cancer treatments. In his famous memoir of 1773 he eliminated numerous hyperplasias from the cancers. The Swede Bierchen (1775) differentiated cancer from scrofula and gumma, Astruc from the cysts (he probably saw Paget's disease). Antoine Louis described cancer of the central nervous system, later studied in more detail by Meckel.

Boerhaave, the leading physician of the eighteenth century, regarded cancer as the consequence of local irritation. This point of view seemed confirmed by Pott's (1775) discovery of the scrotal cancer of chimney sweeps, the first occupational cancer ever described. Description of many others has followed like that of the mule spinners, the Schneeberg pulmonary cancer (1879), the bladder cancer of aniline workers (1895), the X-ray cancer (1902—X-ray treatment of cancer was first applied by T. Sjögren in 1899), the bone cancer of dial-makers (1929). Other cancers have been attributed to chronic irritation by gall-stones, ulcers, or lupus. The first special hospital for cancer patients was opened in Rheims in 1740 and lasted till 1840.

Oncology made a tremendous step forward through the flourishing of pathological anatomy, especially in France, at the beginning of the nineteenth century and the shift from the mere study of organ changes to that of the tissues composing the organs. Bichat, the prematurely departed protagonist of this

development, differentiated stroma and parenchyma in cancers and drew attention to their lobular structure. He discarded the old Greek differentiation of open (ulcerated) and non-ulcerated cancers as irrelevant. Laennec, no less a pathological anatomist than a clinician and diagnostician, divided tumours into homologous ones, the tissues which were analogous to existing tissues, and heterologous ones, that is, those which had no parallels in normal tissues. His 'heterologous' group was composed of tubercles and three forms of cancer: the hard scirrhus, the soft 'encephaloid', and the melanoma. While Laennec believed in the local origin of cancer, such close collaborators of his as G. L. Bayle and Cayol still (1812) adhered to the idea of a dyscrasic cancerous diathesis. The same idea was upheld even thirty years later by the great Vienna pathologist Rokitansky, who also believed that tuberculosis and cancer or malaria and cancer would not be found in the same individual. His humoral ideas were also supported by Cruveilhier's emphasis on the 'cancer-juice'. The influential Broussais opposed Laennec's concept of cancer as a formation *sui generis* in regarding it, like everything else, as the mere aftermath of inflammation. Récamier was not only the reinventor of the speculum and one of the aggressive surgeons of the early nineteenth century, who found justification for their daring cancer operations in the new localism long before the invention of anaesthesia and asepsis, but began the transformation of the old humoral concept of metastasis into our modern notion, accomplished by Hannover. Interest in cancer at the turn of the century is also evidenced by the foundation of a 'Society for Investigating the Nature and Cure of Cancer' in London in 1802 by M. Baillie, R. Willan, J. Abernethy and others, which sent out a very interesting questionnaire, but lapsed after a few years. Innumerable cancer theories originated in the nineteenth century and tried to replace the traditional irritation or virus hypotheses. Velpeau emphasized heredity, Haviland the water, others the soil, diet, city life or luxury.

The first half of the nineteenth century saw also the first North American book on tumours. In 1837 the famous Boston surgeon John Collins Warren, who in 1846 performed the first public operation under ether anaesthesia, published his *Surgical Observations on Tumours with Cases and Operations* (see Michael Pollay: *The First American Book on Tumours*, Thesis, Madison, Wis., 1955). Unlike the leading British author on cancer of the period, W. H. Walshe, who was a humoralist, Warren was a solidist. While in his general concepts Warren followed rather closely his British and French preceptors, he was acclaimed in Europe for his great originality and daring as an operator. He emphasized first the necessity of surgical removal of precancerous lesions.

The decisive turn towards new insights in oncology came with the use of the microscope in pathological anatomy and the interpretation of pathological findings in the light first of the Schleiden-Schwann cell theory, handicapped through the assumption of cell formation from an amorphous blastema, then of the Remak-Virchow cell theory ('*omnis cellula e cellula*'). The trail-blazer of these studies was Johannes Müller with his 1838 book, *Ueber den feineren Bau und die Formen der krankhaften Geschwülste*. Müller undertook the analysis and

classification of tumours in terms of chemistry and cellular microscopy, being conspicuously more successful in the latter than in the former endeavour. Müller found cancer tissues not to be heterologous in the sense of the old Laennec theory, which on the cellular level became the postulate of specific cancer cells by such eminent microscopists as Lebert, Bruch, Vogel and Hannover. These tissues would, according to Müller, be normal in another setting. Müller emphasized the embryonic nature of many tumour tissues, noticed already by Serres in 1832. Müller's work served as the basis for that of his great pupil Rudolf Virchow, probably the most influential oncologist of all times.

Virchow applied his 'cellular pathology', that is, the study of all pathology in terms of cellular change, with unequalled success to oncology. He redefined thus the sarcoma, myoma, fibroma and discovered the myosarcoma, myxoma, psammoma and glioma. He contributed immensely to our knowledge of tumour structure and the stages of tumour formation. Heterology and homology were to him not synonyms of malign and benign. Homologous tumours could be quite dangerous in certain circumstances. Heterologous tumours were not necessarily malignant. Heterology was no formation of something absolutely new and different, but merely heterotopy, heterochrony, or heterometry. With this attitude Virchow became the main and victorious opponent of the 'cancer cell'. When Lebert out of doctrinarism claimed that 'cancroids' (epitheliomata—the notion 'epitheliomata' was created by Hannover) on account of their homology and absence of 'cancer cells' were not malignant and did not metastasize, Virchow and Velpeau were able to prove the contrary.

Virchow was the radical proponent of the local origin of cancer and therewith of modern cancer surgery. He regarded local irritation as the main cause of tumour formation, supported by predisposition. Dyscrasia he practically discounted. He believed that metastases might not always occur by cellular spread, but by secretion of a tumour-provoking substance.

Virchow's major error in oncology was his belief that *all* tumours originated from connective tissue, a formation for which he exhibited a curious scientific-political attachment (see my *Rudolf Virchow*, Madison, 1953). Holland (1843) and Remak (1852) demonstrated the epithelial origin of cancroids, confirming thus histologically the clinical differences noticed by Bayle and Cayol; Remak (1854), Michel (1857), Thiersch (1861) and Waldeyer (1867) showed the epithelial origin of carcinoma. Virchow's pupil Cohnheim fathered in 1868 an embryological theory of cancer formation.

Bacteriology, which furthered medicine as a whole so tremendously in the 1870s and 1880s, had a rather stifling effect on oncology, in so far as innumerable efforts to demonstrate the parasitic origin of cancer failed. The only significant exception is the discovery of a sarcoma producing virus in fowl by Peyton Rous in 1911.

Post-Virchowian oncology has mainly followed certain lines of experimental research, of which we can mention here only the first steps in different directions. A. N. Hanau succeeded first in transplanting cancer in 1889, a technique

attempted earlier by Langenbeck, Follin and Velpeau. (He committed suicide later, when suffering himself from cancer.) L. Loeb (1901) and C. O. Jensen (1903) continued this work in mice. Extravital tissue culture, so important for cancer research, was inaugurated by R. G. Harrison (1907) and Carrel (1911). Maud Slye's studies on hereditary cancer in mice (1913–28) and those of C. Little and associates have become famous.

Johannes Fibiger (1913) produced the first experimental cancer in feeding nematode infested cockroaches to mice. This work has later been reinterpreted as the result of avitaminosis. Yamagiva and Ichikava succeeded in 1916 in producing skin cancer in rabbits through tar application.

Early peaks of biochemical cancer research are Lathrop and Loeb's cancer production by estrogens (1916) and Warburg's work on the metabolism of the cancer cell (1924). None of the many admirable experimental results of the recent past has supported unequivocally one of the possible theories of cancer causation like infection, irritation, or heredity. With the discovery of X-rays and radium in the 1890s the first effective additions to the therapeutic armamentarium against cancer since the time of the ancient Egyptians were made.

Whether there exists an actual increase of cancer in our times has been much debated recently. Is the continuous statistical increase only the result of better registration, of better diagnosis (increase lays mostly in the field of the inaccessible cancer), and of the continuous increase in life expectancy? Or is there a factor *X* in our civilization, which makes for actual increase in cancer and makes cancer the 'symbolic disease' of our times, as leprosy was for the Middle Ages, syphilis for the Renaissance, and cholera for the nineteenth century?

All legitimate scepticism towards cancer statistics leaves the puzzling fact undisputed that there are very large regional and ethnic variations in absolute incidence, localization, sex and age distribution. P. E. Steiner (*Cancer: Race and Geography*, Baltimore, 1954) has assembled extensive new evidence in this respect, which is not in favour of racial causes for these differences, but of external factors. In some cases, like the Kangri or the Betel cancer, these factors are obvious. In others, like the prevalence of skin and liver cancer in Africans, of liver and nasopharyngeal cancer in Asiatics, of cancer of the large intestine in the White, they must remain unknown at the present stage of our knowledge.